

Claims

1. A method for identifying an individual unit of a polymer comprising
transiently moving the individual unit of the polymer relative to a station, the identity
5 of the individual unit being unknown,
detecting a signal arising from a detectable physical change in the unit or the station,
and.
distinguishing said signal from signals arising from exposure of adjacent signal
generating units of the polymer to the station as an indication of the identity of the individual
10 unit.

2. The method of claim 1, wherein the station is an interaction station and wherein
individual units are exposed at the interaction station to an agent that interacts with the
individual unit to produce a detectable electromagnetic radiation signal characteristic of said
15 interaction.

3. The method of claim 1, wherein the station is a signal generation station and the
signal produced is a polymer dependent impulse.

20 4. A method for determining the proximity of two individual units of a polymer of
linked units, comprising:
moving the polymer relative to a station,
exposing individual units to the station to produce a characteristic signal arising from
a detectable physical change in the unit or the station, detecting characteristic signals
25 generated, and
measuring the amount of time elapsed between detecting characteristic signals, the
amount of time elapsed being indicative of the proximity of the two individual units.

5. The method of claim 4, wherein the station is an interaction station and wherein
30 individual units are exposed at the interaction station to an agent that interacts with the
individual unit to produce a detectable electromagnetic radiation signal characteristic of said
interaction.

6. The method of claim 5, wherein the agent is selected from the group consisting of electromagnetic radiation, a quenching source and a fluorescence excitation source.

5 7. The method of claim 4, wherein the station is a signal generation station and the signal produced is a polymer dependent impulse.

8. The method of claim 4, wherein the polymer is a nucleic acid.

10 9. The method of claim 4, wherein the individual units of the polymer are labeled with a fluorophore.

10. The method of claim 4, wherein the two individual units are randomly labeled individual units of the polymer.

15 11. The method of claim 5, wherein the interaction station comprises a nanochannel in a wall material.

12. A method for determining the distance between two individual units of a polymer of linked units comprising:

20 (1) causing the polymer to pass linearly relative to a station,
 (2) detecting a characteristic signal generated as each of the two individual units passes by the station,

 (3) measuring the time elapsed between the signals measured,

25 (4) repeating steps 1, 2 and 3 for a plurality of similar polymers to produce a data set,
and

 (5) determining the distance between the two individual units based upon the information obtained from said plurality of similar polymers by analyzing the data set.

30 13. The method of claim 12, wherein the station is a signal generation station.

09852968-051001

14. The method of claim 13, wherein the characteristic signal is a polymer dependent impulse.

15. The method of claim 12, wherein step (2) comprises measuring an electromagnetic radiation signal generated.

16. The method of claim 12, wherein the plurality of similar polymers is a homogeneous population.

17. The method of claim 12, wherein the plurality of similar polymers is a heterogenous population.

18. The method of claim 12, wherein the plurality of similar polymers is randomly labeled.

19. The method of claim 12, wherein the polymer is a nucleic acid.

20. The method of claim 13, wherein the two linked units are detected at the signal generation station by measuring light emission at the station.

21. The method of claim 12, wherein the steps (1) - (4) are carried out substantially simultaneously.

22. The method of claim 12, wherein the station is an interaction station and the interaction station is a nanochannel.

23. An article of manufacture, comprising:

a wall material having a surface defining a channel,

an agent wherein the agent is selected from the group consisting of an electromagnetic radiation source, a quenching source, a luminescent film layer and a fluorescence excitation source, attached to the wall material adjacent to the channel, wherein the agent is close enough to the channel and is present in an amount sufficient to detectably interact with a

partner compound selected from the group consisting of a light emissive compound, a light accepting compound, radiative compound, and a quencher passing through the channel.

24. The article of claim 23, wherein the agent is an electromagnetic radiation source
5 and wherein the electromagnetic radiation source is a light emissive compound.

25. The article of claim 24, wherein the channel is a microchannel.

26. The article of claim 24, wherein the channel is a nanochannel.

10 27. The article of claim 24, wherein the surface of the wall material defining the microchannel is free of the light emissive compound.

28. The article of claim 24, wherein the light emissive compound is attached to an
15 external surface of the wall material.

29. The article of claim 28, wherein the light emissive compound is attached to a linker which is attached to the external surface of the wall material.

20 30. The article of claim 28, wherein the light emissive compound is concentrated at a region of the external surface of the wall material that surrounds a portion of the channel.

31. The article of claim 28, further comprising a masking layer having openings which allow exposure of only localized areas of the light emissive compound.

25 32. The article of claim 24, further comprising a second light emissive compound different from the first attached to the wall material adjacent to the channel, wherein the light emissive compound is close enough to the channel and is present in an amount effective to detectably interact with a partner light emissive compound passing through the channel.

30 33. The article of claim 28, wherein the external surface of the wall material adjacent to the light emissive compound is a conducting layer.

09852968 051001

34. The article of claim 33, wherein the wall material comprises two layers, the conducting layer and a nonconducting layer.

5 35. The article of claim 28, wherein the wall material comprises at least two layers, a first layer preventing signal generation and a second layer allowing signal generation.

36. The article of claim 28, wherein the external surface of the wall material adjacent to the light emissive compound is a light impermeable layer.

10 37. The article of claim 35, wherein the wall material comprises two layers, the light impermeable layer and a support light permeable layer.

15 38. The article of claim 24, wherein the light emissive compound is embedded in the wall material.

39. The article of claim 38, wherein the light emissive compound is concentrated at a region of the wall material that surrounds a portion of the channel.

20 40. The article of claim 39, wherein the light emissive compound forms a concentric ring in the wall material around a portion of the channel.

25 41. The article of claim 38, further comprising a second light emissive compound different from the first attached to the wall material adjacent to the channel, wherein the light emissive compound is close enough to the channel and is present in an amount effective to detectably interact with a partner light emissive compound passing through the channel.

30 42. The article of claim 41, wherein the second light emissive compound is embedded in the wall material.

43. The article of claim 38, wherein the wall material comprises a first conducting layer adjacent to a first side of the light emissive compound.

09852968-051001
"00750" 89625860

44. The article of claim 43, wherein the wall material comprises a second conducting layer adjacent to a second side of the light emissive compound, the first and second layers sandwiching the light emissive compound.

5

45. The article of claim 38, wherein the wall material comprises a nonconducting material and wherein the light emissive compound is embedded in the nonconducting material.

10

46. The article of claim 38, wherein the wall material comprises a first light impermeable layer on a first side of the light emissive compound.

15

47. The article of claim 46, wherein the wall material comprises a second light impermeable layer on a second side of the light emissive compound, the first and second layers sandwiching the light emissive compound.

48. The article of claim 38, wherein the wall material is a light permeable material.

20

49. The article of claim 48, wherein the light emissive compound is embedded in the light permeable material.

50. The article of claim 24, wherein the light emissive compound is embedded in a layer of a light permeable material.

25

51. The article of claim 44, wherein the light emissive compound is embedded in a layer of a light permeable material.

52. The article of claim 23, wherein the light emissive compound is a fluorescent compound.

30

53. The article of claim 24, wherein a length of the nanochannel is between 500 Angstroms and 1 mm.

09852968 051001

54. The article of claim 23, wherein a width of the channel is between 1 and 500 Angstroms.

5 55. The article of claim 23, wherein the wall material is formed of two layers, a first light impermeable layer and a luminescent film layer attached to one another, wherein the channel extends through both layers and is defined by surfaces of both layers.

56. The article of claim 55, wherein the channel is a nanochannel.

10 57. The article of claim 56, further comprising a second light impermeable layer, the luminescent film layer positioned between the first and second light impermeable layers.

15 58. The article of claim 55, wherein the surface defining the channel includes a surface of the light impermeable layer which is free of luminescent film layer material.

59. The article of claim 55, wherein the length of the channel is between 500 Angstroms and 1 mm.

20 60. The article of claim 23, wherein the agent is a fluorescence excitation source and wherein the fluorescence excitation source is a scintillation layer.

25 61. The article of claim 60, wherein the scintillation layer is selected from the group consisting of NaI(Tl), ZnS(Ag), anthracene, stilbene, and plastic phosphors.

62. The article of claim 60, wherein the scintillation layer is embedded in the wall material between two radiation impermeable layers.

30 63. An article of manufacture, comprising:
a wall material having a surface defining a plurality of channels,
a station attached to a discrete region of the wall material adjacent to at least one of the channels, wherein the station is close enough to the channel and is present in an amount

09852968 051001

sufficient to cause a signal to arise from a detectable physical change in a polymer of linked units passing through the channel or in the station as the polymer is exposed to the station.

64. The article of claim 63, wherein the station is an interaction station and wherein
5 the interaction station is an electromagnetic radiation source.

65. The article of claim 63, wherein the wall material is formed of two layers, a first
light impermeable layer and a luminescent film layer attached to one another, wherein the
channel extends through both layers and is defined by surfaces of both layers.

66. The article of claim 63, wherein the station is a signal generation station and
wherein the signal generation station produces a polymer dependent impulse.

67. The article of claim 63, wherein the station is an electromagnetic radiation source
15 and
wherein the electromagnetic radiation source is a scintillation film.

68. The article of claim 67, wherein the scintillation film is embedded in the wall
material between two radiation impermeable layers.

69. The article of claim 64, wherein the channel is a microchannel.

70. The article of claim 64, wherein the channel is a nanochannel.

71. An article of manufacture, comprising:
a wall material having a surface defining a channel,
a plurality of stations each attached to a discrete region of the wall material adjacent
to the channel, wherein the stations are close enough to the channel and are present in an
amount sufficient to cause a signal to arise from a detectable physical change in a polymer of
30 linked units passing through the channel or in the station as the polymer is exposed to the
station.

09852958 "051001
T00T50" 89625860

72. The article of claim 71, wherein the stations are interaction stations.

73. The article of claims 71, wherein the stations are signal generation stations.

5 74. The article of claim 71, wherein the station is an electromagnetic radiation source and wherein the electromagnetic radiation source is a scintillation film.

75. The article of claim 71, wherein the channel is a microchannel.

10 76. The article of claim 71, wherein the channel is a nanochannel.

77. A method for preparing a wall material comprising covalently bonding light emissive compounds or quenching compounds to a plurality of discrete locations of a wall material, each of said discrete locations close enough to a respective interaction station on
15 said wall material, whereby when an individual unit of a polymer, which is interactive with said light emissive compound or quenching compound to produce a signal, is positioned at said interaction station, the light emissive compound or the quenching compound interacts with the individual unit to produce said signal.

20 78. The method of claim 77, wherein the light emissive compounds or quenching compounds are covalently bonded at discrete locations close to channels in said wall material, said channels defining interaction stations.

25 79. The method of claim 78, wherein the channels are nanochannels.

80. The method of claim 78, wherein the channels are microchannels.

81. The method of claim 78, wherein the light emissive compounds or quenching compounds are covalently bonded to the wall material in a manner whereby the surfaces of
30 the wall material defining the channel are free of the light emissive compounds and quenching compounds.

09352968 "051001

82. The method of claim 79, wherein the light emissive compounds or quenching compounds are covalently bonded to the wall material in a manner whereby the surfaces of the wall material defining the channel are free of the light emissive compounds and quenching compounds.

5

83. The method of claim 79 further comprising applying a layer of conductive material to said wall material.

84. A method for attaching a chemical substance selectively at a rim of a channel
10 through a wall material that is opaque comprising:
providing a wall material with photoprotective chemical groups attached at the rim of the channel through the wall material,
applying light to the photoprotective chemical groups to dephotoprotect the chemical groups, and
15 attaching the chemical substance to the deprotected chemical groups.

85. The method of claim 84, wherein the light is applied to only selected regions of a surface of the wall material defining the rim of the channel.

20 86. The method of claim 84, wherein the channel has a first end and a second end, the rim being at the first end, and wherein the light is applied to the second end, the light passing through the channel to contact the photoprotected chemical groups at the rim of said first end.

25 87. The method of claim 84, wherein the channel is a microchannel.

88. The method of claim 84, wherein the channel is a nanochannel.

89. A method for preparing a wall material having localized areas of light emission on a surface of the wall material comprising:

30 providing a wall material having a surface, and
applying a light emissive compound to the surface to produce at least localized areas of light emission on the surface, wherein the localized areas define a target region for

detecting light emission, and wherein the target region is a rim of a channel through the wall material.

90. The method of claim 89, further comprising the steps of attaching a photoprotective chemical group to the surface of the wall material, applying light to the photoprotective chemical groups to dephotoprotect the chemical groups prior to attaching the light emissive compound, and attaching the light emissive compound to the dephotoprotected chemical groups.

91. The method of claim 90, wherein the light is applied to only selected regions of the surface of the wall material defining the rim of the channel.

92. The method of claim 90, wherein the photoprotective chemical group is attached to only selected regions of the surface of the wall material defining the rim of the channel.

93. The method of claim 90, wherein the channel has a first end and a second end, the rim being at the first end, and wherein the light is applied to the second end, the light passing through the channel to contact the photoprotected chemical groups at the rim of said first end.

94. The method of claim 90, wherein the channel is a microchannel.

95. The method of claim 90, wherein the channel is a nanochannel.

96. The method of claim 89, further comprising the step of positioning a mask having openings over the surface of the wall material such that only localized areas of light emission are exposed through the openings of the mask.

97. The method of claim 96, wherein the light emissive compound is attached to a portion of the surface of the wall material.

98. A method for detecting resonance energy transfer or quenching between two interactive partners capable of such transfer or quenching comprising

bringing the two partners in close enough proximity to permit such transfer or quenching,

applying an agent to one of said partners, the agent selected from the group consisting of electromagnetic radiation, a quenching source and a fluorescence excitation source,

5 shielding fluorescence resonance energy transfer and quenching occurring from electromagnetic radiation emission and interaction between said partners with a material shield, and

detecting the emitted electromagnetic radiation.

10 99. An apparatus for detecting a signal comprising,

a housing with a buffer chamber

a wall defining a portion of the buffer chamber, and having a plurality of openings for aligning polymers,

15 a sensor fixed relative to the housing, the sensor distinguishing the signals emitted at each opening from the signals emitted at the other of the openings to generate opening dependent sensor signals, and

a memory for collecting and storing said sensor signals.

20 100. The apparatus of claim 99, wherein the sensor is an optical sensor and the optical sensor senses electromagnetic radiation signals emitted at the plurality of openings.

101. The apparatus of claim 99, further comprising a microprocessor.

25 102. The apparatus of claim 99, wherein the openings are defined by microchannels in the wall.

103. The apparatus of claim 99, wherein the openings are defined by nanochannels in the wall.

30 104. The apparatus of claim 99, wherein the plurality is at least 50.

09852958-051001

105. The apparatus of claim 99, wherein the apparatus further comprises a second buffer chamber separated from said first buffer chamber, by said wall, and wherein the buffer chambers are in fluid communications with one another via the openings.

5 106. The apparatus of claim 104, wherein the apparatus further comprises a second buffer chamber separated from said first buffer chamber, by said wall, and wherein the buffer chambers are in fluid communications with one another via the openings.

10 107. The apparatus of claim 105 further comprising a pair of electrodes secured to the housing, one of said pair positioned in the first buffer chamber and the other of the pair positioned in the second buffer chamber.

108. An apparatus for detecting a signal comprising
a housing defining a first buffer chamber and a second buffer chamber,
15 a wall supported by the housing and separating the first and second buffer chambers,
a plurality of channels defined by the wall and providing fluid communications
between the first and second buffer chambers, and
a sensor for distinguishing and collecting channel dependent signals.

20 109. The apparatus of claim 108, wherein the channels are nanochannels.

110. The apparatus of claim 108, wherein the channels are microchannels.

25 111. The apparatus of claim 108, wherein an agent selected from the group consisting of electromagnetic radiation, a quenching source and a fluorescence excitation source is attached to the wall.

112. The apparatus of claim 111, wherein the agent is electromagnetic radiation and wherein the electromagnetic radiation is a light emissive compound

30 113. The apparatus of claim 112, wherein the light emissive compound is concentrated at the channels in the wall.

09852968 051001

114. The apparatus of claim 108 further comprising means for moving biological entities through the channels.

5 115. A method for characterizing a test polymer comprising,
obtaining polymer dependent impulses for a plurality of polymers,
comparing the polymer dependent impulses of the plurality of polymers,
determining the relatedness of the polymers based upon similarities between the
polymer dependent impulses of the polymers, and
10 characterizing the test polymer based upon the polymer dependent impulses of related
polymers.

116. The method of claim 115, wherein the plurality of polymers is a homogenous
population.

15 117. The method of claim 115, wherein the plurality of polymers is a heterogeneous
population.

118. The method of claim 115, wherein the polymer is randomly labeled.

20 119. The method of claim 115, wherein the polymer is a polymer of at least two
different linked units, and wherein said at least two different linked units are labeled to
produce different signals.

25 120. The method of claim 115, wherein the polymer is a nucleic acid.

121. The method of claim 120, wherein the obtained polymer dependent impulses
include an order of polymer dependent impulses.

30 122. The method of claim 120, wherein the obtained polymer dependent impulses
includes the time of separation between specific signals.

05852968-051001

123. The method of claim 120, wherein the polymer dependent impulses are obtained by moving the plurality of polymers lineally past a signal generation station.

124. The method of claim 120, wherein the obtained polymer dependent impulses
5 include a number of polymer dependent impulses.

125. A method for labeling nucleic acids comprising,
contacting a dividing cell with a nucleotide analog,
isolating from the cell nucleic acids that have incorporated the nucleotide analog, and
10 modifying the nucleic acid with incorporated nucleotide analog by labeling the
incorporated nucleotide analog.

126. The method of claim 125, wherein the nucleotide analog is a brominated analog.

127. The method of claim 125, wherein the dividing cell is contacted with a
15 nucleotide analog by
growth arresting the cell in the cell division cycle,
performing the contacting step, and
allowing the cell to reenter the cell division cycle.

128. The method of claim 125, wherein the nucleic acids are isolated after the cells
20 have reentered and completed the cell division cycle and before a second cell division cycle
is completed.

129. The method of claim 125, wherein the incorporated nucleotide analog is labeled
25 with an agent selected from the group consisting of an electromagnetic radiation source, a
quenching source, a fluorescence excitation source, and a radiation source.

130. A method for determining the order of units of a polymer of linked units
30 comprising:

(1) moving the polymer linearly relative to a station,

098295 051001
FOOT 50 89625860

(2) measuring a polymer dependent impulse generated as each of two individual units, each giving rise to a characteristic signal, pass by the station,

(3) repeating steps 1 and 2 for a plurality of similar polymers, and

(4) determining the order of at least the two individual units based upon the information obtained from said plurality of similar polymers.

131. The method of claim 130, wherein the station is a signal generation station.

132. The method of claim 130, wherein the station is an interaction station.

133. The method of claim 130, wherein step (2) comprises measuring an electromagnetic radiation signal generated.

134. The method of claim 130, wherein the plurality of similar polymers is a homogeneous population.

135. The method of claim 130, wherein the plurality of similar polymers is a heterogenous population.

136. The method of claims 130, wherein the polymer is a nucleic acid.

137. A method for analyzing a set of polymers, each polymer of said set being an individual polymer of linked units comprising:

orienting the set of polymers parallel to one another, and

detecting a polymer specific feature of said polymers.

138. The method of claim 137, wherein the polymers are oriented by applying an electric field to said polymers.

139. The method of claim 137, wherein the polymer specific feature is an order of linked unity in the polymers.

140. The method of claim 137, wherein the detecting step is performed simultaneously for said polymers.

141. The method of claim 137, wherein the detection step comprises measuring electromagnetic radiation signals.

142. The method of claim 137, wherein the detection step comprises causing the polymers to pass linearly relative to a plurality of signal generation stations, and detecting and distinguishing signals generated as said polymers pass said interaction stations.

143. The method of claim 137, wherein the polymers are a homogenous population.

144. The method of claim 137, wherein the polymers are a heterogenous population.

145. The method of claim 137, wherein the polymers are randomly labeled.

146. The method of claim 137, wherein the orientation step is in a solution free of gel.

147. A method for analyzing a set of polymers, each polymer of the set being an individual polymer of linked units, comprising:
orienting the set of polymers in an electric field,
simultaneously moving the set of polymers through defined respective channels, and
detecting a polymer specific feature as the polymers are moved through the channels.

148. The method of claim 147 wherein the channels are nanochannels.

149. The method of claim 147, wherein the polymer specific feature is an order of linked unity in the polymers.

150. The method of claim 147, wherein the detecting step is performed simultaneously for said polymers.

151. The method of claim 147, wherein the detection step comprises measuring electromagnetic radiation signals.

5 152. The method of claim 147, wherein the detection step comprises causing the polymers to pass linearly relative to a plurality of signal generation stations, and detecting and distinguishing polymer dependent impulses generated as said polymers pass said signal generation stations.

10 153. The method of claim 147, wherein the polymers are a homogenous population.

154. The method of claim 147, wherein the polymers are a heterogenous population.

155. The method of claim 147, wherein the polymers are randomly labeled.

15 156. The method of claim 147, wherein the orientation step is in a solution free of gel.

20 157. An apparatus for detecting optically a plurality of signals comprising:
a housing with a buffer chamber,
a wall material defining a portion of the buffer chamber, the wall including polymer interaction stations, and
an optical sensor secured to the housing, the optical sensor constructed and arranged to detect electromagnetic radiation signals emitted at the interaction stations.

25 158. A computer system for making characteristic information of a plurality of polymers of linked units available in response to a request, comprising:
a memory for storing, for each of the plurality of the polymers and in a manner accessible using a unique identifier for the polymer, records including information indicative
30 of sequentially detected signals arising from a detectable physical change in the plurality of individual units of the polymer or a station to which the polymer is exposed; and

a processor for accessing the records stored in the memory for a selected one of the plurality of the polymers according to a unique identifier associated with the selected polymer.

5 159. The system of claim 158, wherein the sequentially detected signals arise from an interaction of the plurality of individual units of the polymer exposed to an agent selected from the group consisting of electromagnetic radiation, a quenching source and a fluorescence excitation source

10 160. The computer system of claim 158, further comprising:
 means for comparing the sequentially detected signals of the selected polymer to a known pattern of signals characteristic of a known polymer to determine relatedness of the selected polymer to the known polymer.

09852568 051001